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| 10/537,971 | 06/09/2005 | Yoshihiro Ohmiya | | 8735 |

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| EXAMINER | |
|---|---|
| NOAKES, SUZANNE MARIE | |
| ART UNIT | PAPER NUMBER |
| 1656 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/537,971 | OHMIYA ET AL. | |
| | Examiner | Art Unit | |
| | SUZANNE M. NOAKES | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

1. The amendments and remarks filed 20 August 2008 are acknowledged. Applicants have cancelled claims 1-15, 18-21 and 26. Thus, claims 16, 17 and 22-25 are pending and subject to Examination on the merits.

### *Withdrawal of Rejections/Objections*

2. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

3. The objection to the Drawings/Specification as it pertained to Compliance with the Sequence Rules is withdrawn in view of the amendments to the specification filed 08 February 2008.

4. The objection to claims 16 and 17 for containing non-elected subject matter is withdrawn in view of the amendments to the claims filed 08 February 2008 and 20 August 2008.

5. The rejection of claims 16 and 17 for lacking Written Description under 35 U.S.C. 112 1st paragraph, as recited in the previous Non-Final Office action (10 September 2007, Section 8) is withdrawn in view the amendments to the claims. It should be noted that a new Written Description rejection as it pertains to the instant claims, however, has been introduced which has been necessitated by amendments to the claims.

6. The rejection of claims 16 and 17 for lacking Enablement under 35 U.S.C. 112 1st paragraph, as recited in the previous Non-Final Office action (10 September 2007,

Section 9) is withdrawn in view of further reconsideration. It is noted that introducing methods of introducing proteins into cells is well within the knowledge and skill of those in the instant art. It should be noted, however, that a new Enablement rejection, however, as it pertains to the instant claims has been introduced which has been necessitated by amendments to the claims.

***Claim Rejections - 35 USC § 112 – 2nd paragraph***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 25 recites the limitation "wherein the monitor protein is represented by a base sequence in SEQ ID NO: 2" in reference to claim 16 which recites a method of measuring a processing ability of a certain cell, said method comprising introducing a monitor protein that comprises: i) a secretory *Cypridina nocitluca* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP). There is insufficient antecedent basis for this limitation in the claim because SEQ ID NO: 2 does not contain a secretory *Cypridina nocitluca* luciferase, rather the luciferase found within SEQ ID NO: 2 is from *Vargula hilgenderfi* and NOT *Cypridina nocitluca* as evidenced by the sequence alignment of the first 555 amino acids of SEQ ID NO: 2 shown below and found in SCORE (see 06/22/2007 result 5 - .rag file)

```
RESULT 5
AAR11108
ID   AAR11108 standard; protein; 555 AA.
XX
```

AC AAR11108;
XX
DT 25-MAR-2003 (revised)
DT 23-MAY-1991 (first entry)
XX
**DE Luciferase deduced from cDNA.**
XX
KW luciferin; luminescence.
XX
**OS Vargula hilgendorfii.**
XX
PN JP03030678-A.
XX
PD 08-FEB-1991.
XX
PF 29-JUN-1989; 89JP-00167689.
XX
PR 29-JUN-1989; 89JP-00167689.
XX
PA (OSAB-) OSAKA BIOSCIENCE KENKYUSHU KK.
XX
DR WPI; 1991-084343/12.
DR N-PSDB; AAQ10957.
XX
**PT DNA cpd. coding luciferase derived from vargula hilgendorfii - by**
**PT transfection of host cells and culturing.**
XX
PS Claim 1; Fig 3; 11pp; Japanese.
XX
CC The cDNA encoding the protein is used to prepare vector pRSVVL which is
CC used to transfect COS cells (ATCC CRL1650) for expression of luciferase.
CC The enzyme is useful for assays in biomedical or enviromental fields.
CC (Updated on 25-MAR-2003 to correct PA field.)
XX
SQ Sequence 555 AA;

Query Match 67.3%; Score 3029; DB 2; Length 555;
Best Local Similarity 100.0%; Pred. No. 1.5e-252;
Matches 555; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 MKIIILSVILAYCVTDNCQDACPVEAEPPSSTPTVPTSCEAKEGECIDTRCATCKRDILS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MKIIILSVILAYCVTDNCQDACPVEAEPPSSTPTVPTSCEAKEGECIDTRCATCKRDILS 60

Qy         61 DGLCENKPGKTCCRMCQYVIECRVEAAGYFRTFYGKRFNFQEPGKYVLARGTKGGDWSVT 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 DGLCENKPGKTCCRMCQYVIECRVEAAGYFRTFYGKRFNFQEPGKYVLARGTKGGDWSVT 120

Qy        121 LTMENLDGQKGAVLTKTTLEVAGDVIDITQATADPITVNGGADPVIANPFTIGEVTIAVV 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 LTMENLDGQKGAVLTKTTLEVAGDVIDITQATADPITVNGGADPVIANPFTIGEVTIAVV 180
```

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Qy        181 EIPGFNITVIEFFKLIVIDILGGRSVRIAPDTANKGLISGICGNLEMNDADDFTTDADQL 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 EIPGFNITVIEFFKLIVIDILGGRSVRIAPDTANKGLISGICGNLEMNDADDFTTDADQL 240

Qy        241 AIQPNINKEFDGCPFYGNPSDIEYCKGLMEPYRAVCRNNINFYYYTLSCAFAYCMGGEER 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 AIQPNINKEFDGCPFYGNPSDIEYCKGLMEPYRAVCRNNINFYYYTLSCAFAYCMGGEER 300

Qy        301 AKHVLFDYVETCAAPETRGTCVLSGHTFYDTFDKARYQFQGPCKEILMAADCYWNTWDVK 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 AKHVLFDYVETCAAPETRGTCVLSGHTFYDTFDKARYQFQGPCKEILMAADCYWNTWDVK 360

Qy        361 VSHRDVESYTEVEKVTIRKQSTVVDLIVDGKQVKVGGVDVSIPYSSENTSIYWQDGDILT 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 VSHRDVESYTEVEKVTIRKQSTVVDLIVDGKQVKVGGVDVSIPYSSENTSIYWQDGDILT 420

Qy        421 TAILPEALVVKFNFKQLLVVHIRDPFDGKTCGICGNYNQDSTDDFFDAEGACALTPNPPG 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 TAILPEALVVKFNFKQLLVVHIRDPFDGKTCGICGNYNQDSTDDFFDAEGACALTPNPPG 480

Qy        481 CTEEQKPEAERLCNNLFDSSIDEKCNVCYKPDRIARCMYEYCLRGQQGFCDHAWEFKKEC 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 CTEEQKPEAERLCNNLFDSSIDEKCNVCYKPDRIARCMYEYCLRGQQGFCDHAWEFKKEC 540

Qy        541 YIKHGDTLEVPPECQ 555
              |||||||||||||||
Db        541 YIKHGDTLEVPPECQ 555
```

Thus, SEQ ID NO: 2, as noted does not contain any a secretory *Cypridina nocitluca* luciferase and as such claim 25 lacks antecedent basis.

### *Claim Rejections - 35 USC § 112 – 1st paragraph*

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Written Description:*

10. Claims 16, 17 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of measuring a processing ability of a certain cell, said method comprising introducing a monitor protein that comprises: i) a secretory *Cypridina noctiluca* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP). The claims are thus interpreted that the secretory luciferase from *Cypridina noctiluca* is one which naturally occurs in said organism and which has been isolated from said organism. However, it is noted that the entire specification is drawn to a difference luciferase isolated from *Vargula hilgendorfii*. The specification states:

> The protein of the present invention can be obtained by incorporating the gene of the present invention described later into the expression vector and expressing it in appropriate host cells. As the expression vector, for example, pBT-VL-mp-YFP (**VLuc**, mp and YFP indicate ***Cypridina noctiluca* luciferase**, a monitor peptide and the yellow fluorescent protein, respectively) and the like can be used. (see p. 13, lines 27-33).

Examples 1-4 are drawn to "Vluc" chimeric fusion proteins. However, there appears to be absolutely no isolation of a gene or protein of any luciferase from the species ***Cypridina noctiluca*** anywhere in the specification. As noted above in the 112 2nd paragraph rejection, even the preferred embodiment which is to represent a monitor protein a secretory *Cypridina noctiluca* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP) clearly does not possess a luciferase from this organism. The luciferase is from the well known *Vargula hilgendorfii* and it is known that these two luciferase only share 83.1% sequence identity (see

Nakajima et al. Biosci. Biotechnol. Biochem. 2004, 68(3):565-570 - Abstract and Figure 2). However, the courts have established that the disclosure of a partial structure, and in this case no structure, without additional characterization of the product may not be sufficient to evidence possession of the claimed invention. See, e.g., Amgen Inc. V. Chugai Pharmaceutical Co. Ltd, 927 F.2d at 1206, 18 USPQ2d at 1021 which states:

> "A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated.") (citations omitted).

Thus, while one might be in possession of the idea that this organism might possess a luciferase and it might be obtainable by using stringent hybridization assays utilizing the luciferase from other organisms, this is not enough to provide evidence that Applicants were in possession of a monitor protein comprising: i) a secretory *Cypridina noctiluca* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP) which is used in the instant methods.

*Enablement:*

11. Claims 16, 17, 22-25 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The following is noted from MPEP chapter 2100:

> "Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, ***when filed***, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." MPEP 2164.01 and 2165.05(a)

The instant claims are drawn to method of using a monitor protein comprising: i) a secretory *Cypridina noctiluca* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP) which is used in the instant methods. However, as noted above, the specification does not describe any luciferase from *Cypridina noctiluca*. While it purports one exists, and that it can be exemplified by the sequence described in SEQ ID NO: 1 for the DNA and the protein it encodes of SEQ ID NO:2, it also evident that these sequences disclose a luciferase from a completely different organism (*Vargula hilgendorfii* – as evidenced by the Patent Office sequence alignment disclosed above in the 112 2nd paragraph rejection as well as the Nakajima et al. 2004 reference). Thus, Applicants were not in possession of a monitor protein comprising : i) a secretory *Cypridina noctiluca* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP) which is used in the instant methods; rather it was in possession of a monitor protein comprising: i) a secretory *Vargula hilgendorfii* luciferase; ii) a processing cleavage region of 10-40 amino acids and iii) a yellow fluorescent protein (YFP) to be used in the claimed method. It is noted, however, that one skilled in the art is not even apprised as to whether *Cypridina noctiluca* would contain such an enzyme and even if they did, despite the specification saying it does exist; it clearly has not been isolated at the time of filing. Thus, there would be the expectation of a considerable amount of undue experimentation imposed on one skilled in the art to try to isolate the appropriate gene, clone it and then make it into Applicants claimed monitor protein to be used in the claimed invention. While the skill level is quite high in the art, the requirement of

applicants to be in possession of the claimed invention at the time of filing evidently lacking and as such Applicants are not enabled for the method as claimed.

***Conclusion***

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656
24 November 2008